THOMAS FRANCIS, JR., M. D.

SER. II, VOL. 12 *February, 1950* No. 4

# TRANSACTIONS OF THE NEW YORK ACADEMY OF SCIENCES

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## *Contents*

Studies on Pteroylglutamic Acid Inhibitors. *By* J. J. OLESON 118

Thematic Apperception: Failures and the Defenses. *By* LEOPOLD BELLAK 122

The Mexican Calendar and the Founding of Tenochtitlan-Tlatelolco. *By* PAUL KIRCHHOFF 126

The Relationship of *In Vitro* Tests of Antifungal Substances to Therapeutic Problems. *By* K. A. OSTER AND M. J. GOLDEN 132

A. Cressy Morrison Prize Competition for 1950 137

New Members 137

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TRANSACTIONS of The New York Academy of Sciences, Series II, Volume 12, No. 4, February, 1950.
Entered as second-class matter December 12, 1947, at the post office at Baltimore, Maryland, under the act of August 24, 1912. This publication is distributed to members and is published monthly from November to June, inclusive, by The New York Academy of Sciences, Mt. Royal and Guilford Aves., Baltimore 2, Md. Editorial office: Seventy-Ninth Street and Central Park West, New York 24, N. Y.

*Executive Director:* EUNICE THOMAS MINER

## *SECTION OF BIOLOGY**

# STUDIES ON PTEROYLGLUTAMIC ACID INHIBITORS†

*By* J. J. OLESON‡

The use of biologically important substances, and derivatives prepared therefrom, often extends beyond their function as originally discovered when a sufficient quantity of a variety of related compounds becomes available for diverse research and clinical investigations. One example of this is pteroylglutamic acid (PGA) and its derivatives. Originally a growth factor for bacteria and chickens, these compounds are now being used for the treatment of a variety of macrocytic anemias and neoplastic diseases and in fundamental biological work on many species. We shall present here a few experiments on a limited number of derivatives and some nutrition experiments involving some of them.

TABLE 1

THE ACTIVITY OF VARIOUS PGA DERIVATIVES FOR CHICK GROWTH

| *Active compounds* | *Inactive compounds* |
|---|---|
| pteroylglutamic acid | "Hydrolysis" products of PGA |
| pteroyldiglutamic acid | pteroyl d(−) glutamic acid |
| pteroyltriglutamic acid | pteroylserylglutamic acid |
| pteroylhexaglutamic acid | pteroylaspartic acid |
| pteroylglutamyl glycine | pteroyl α aminopimelic acid |
| pteroylglutamyl-β alanine | pteroyl (dl) threonine |
| formyl pteroylglutamic acid | 2,4 dihydroxy pteroylglutamic acid |
| N-10 nitroso pteroylglutamic acid | 7 hydroxy pteroylglutamic acid |
| | 7 methylpteroylglutamic acid |
| | 9 methylpteroylglutamic acid |
| | 9-10 dimethylpteroylglutamic |
| | thymine |
| | xanthopterin |
| | pteroic acid |

TABLE 2

COMPARISON OF PGA INHIBITORS

| *Strong* (*10-100 γ/day*) | *Moderate* (*100 γ-1 mg./day*) |
|---|---|
| 4 aminopteroylglutamic acid (aminopterin) | 4 aminopteroylaspartic acid |
| 4 aminopteroyltriglutamic acid | 4 aminopteroyl α alanine |
| 4 aminopteroylglutamyl glycine | 4 aminopteroyl threonine |
| 4 aminopteroylglutamyl β alanine | 9-10 dimethylpteroylglutamic acid |
| 4 amino 9 methylpteroylglutamic acid | 6 methyl 7 pteroylglutamic acid |
| 4 amino 9-10 dimethylpteroylglutamic acid | 7 methylpteroylglutamic acid |
| | 4 aminopteroylserylglutamic acid |

*Weak or Inactive* (*>1 mg./day*)

pteroylaspartic acid
4 dimethylaminopteroyl glutamic acid
pteroyl d(−) glutamic acid
pteroylserylglutamic acid
dichloropteroylglutamic acid
2,4 dihydroxy pteroylglutamic acid
N-10 nitroso aminopterin

The relation of structure to growth promoting activity in chicks fed a synthetic PGA-deficient diet is shown in TABLE 1. As is well known, the intact pteroylglutamyl moiety is essential for activity.

* The Section of Geology and Mineralogy held a meeting on Jan. 2, 1950, at which Robert L. Nichols, Tufts College, Medford, Mass., presented a paper entitled "Beyond the Arctic and Antarctic Circles," illustrated with Kodachrome slides. No abstract of this paper has been received.

† This paper, illustrated with lantern slides, was presented at the meeting of the Section on January 9, 1950.

‡ Lederle Laboratories Division, American Cyanimid Company, Pearl River, N. Y.

TABLE 3

EFFECT OF $B_{12}$ ON REVERSAL OF ANTAGONIST

| Group | Supplement to basal diet | Avt. wt. & no. alive (—) 0 weeks Initial | 1 | 2 | 3 |
|---|---|---|---|---|---|
| 1 | none | 41 (8) | 62 | 74 | 81 (6) |
| 2 | 5 γ PGA | 41 (8) | 79 | 134 | 212 |
| 3 | 25 γ PGA | 41 (8) | 81 | 127 | 196 |
| 4 | 0.2 γ $B_{12}$ | 41 (8) | 76 | 97 (7) | 114 (4) |
| 5 | 0.2 γ $B_{12}$ + 5 γ PGA | 40 (8) | 79 | 139 | 218 |
| 6 | 0.2 γ $B_{12}$ + 25 γ PGA | 40 (8) | 77 | 131 | 209 |
| 7 | none | 41 (8) | 70 | 86 (4) | 90 (2) |
| 8 | 5 γ PGA | 40 (8) | 76 | 133 | 191 |
| 9 | 25 γ PGA | 41 (8) | 77 (6) | 137 | 198 |
| 10 | 0.2 γ $B_{12}$ | 41 (8) | 77 | 107 | 104 |
| 11 | 500 γ 4 aminopteroylaspartic acid | 44 (8) | 53 | 72 (1) | — (0) |
| 12 | as 11 + 5 γ PGA | 44 (8) | 62 | 91 (7) | 91 (7) |
| 13 | as 11 + 25 γ PGA | 44 (8) | 72 | 126 | 178 |
| 14 | as 11 + 0.2 γ $B_{12}$ | 44 (8) | 59 (7) | 61 (6) | 52 (1) |
| 15 | as 11 + 0.2 γ $B_{12}$ + 5 γ PGA | 43 (8) | 69 | 106 (6) | 163 (6) |
| 16 | as 11 + 0.2 γ $B_{12}$ + 25 γ PGA | 43 (8) | 79 | 141 | 212 (8) |

Alteration of the amino acid portion or the 2 amino or 4 hydroxy groups inactivates

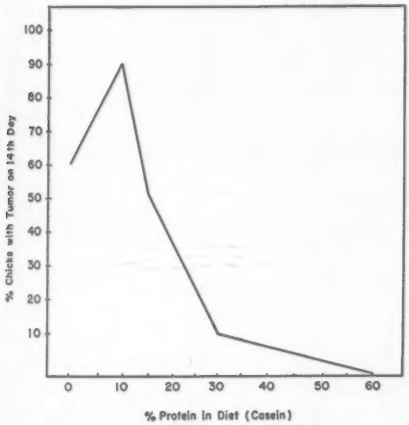


FIGURE 1. Effect of protein on growth of Rous.

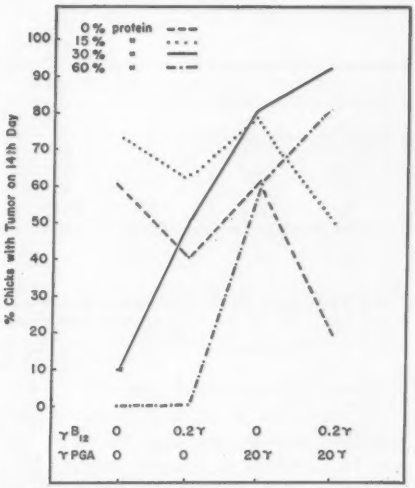


FIGURE 2. Effect of PGA and $B_{12}$ on Rous in chicks fed various protein levels.

the compound, as does the introduction of methyl groups at various positions. Addition of other amino acids, in peptide linkage to the molecule, gives active compounds, but interposing a different amino acid between the pteroic and glutamic acids does result in inactivity. It is of interest that the N-10 formyl and N-10 nitroso substituents yield fully active compounds.

Certain changes in the structure of PGA produce extremely potent antagonists which are reversed by proper levels of the vitamin, albeit with difficulty in some cases. TABLE 2 lists some compounds tested as inhibitors using the growth of chicks and rats. They are arbitrarily listed in 3 groups according to the amount of compound necessary to produce inhibition of growth.

The most potent inhibitors are those containing the 4 aminopteroylglutamyl moiety. Conjugation with other amino acids or addition of methyl groups does not markedly weaken the 4 amino type of compounds. However, the substitution of

other amino acids for the glutamic acid in the 4 amino series somewhat lessens their inhibitory potency. The methylated PGA derivatives are moderately active for chicks but very weak for rats, which are less susceptible to these compounds. It is interesting that the 4 dimethylamino and the N-10 nitroso derivatives of aminopterin are inactive as antagonists.

The inhibitors just mentioned are completely reversed by PGA alone. When vitamin $B_{12}$ is given to chicks, however, the amount of PGA required for this reversal is markedly reduced. TABLE 3 gives a typical example. Vitamin $B_{12}$ alone has little effect in supplementing the growth effect of PGA on the diet used, a typical synthetic diet containing 30 per cent protein (group 1–6). Chicks given 500γ of 4 aminopteroylaspartic acid failed to survive. A slight reversal occurred with 5γ of PGA and complete reversal was ob-

TABLE 4

THE INHIBITORY EFFECT OF 4-AMINO COMPOUNDS ON THE ACTIVITY OF PTEROYLGLUTAMIC ACID IN GROWTH OF ROUS SARCOMA

| *Compound* | *Am't inj. daily/am't of PGA* | *Total no. of chicks* | *% chicks w. tumors* | *Avg. tumor size* |
|---|---|---|---|---|
| 4-Aminopteroylglutamic acid (Aminopterin) | 10 γ/10 γ | 0 (10*) | — | — |
| | 10 γ/250 γ | 6 (10*) | 83 | ++ |
| 4-Aminopteroylglutamyl glycine | 10 γ/10 γ | 2 (10*) | 0 | 0 |
| | 25 γ/10 γ | 0 (10*) | — | — |
| 4-Aminopteroylglutamyl β alanine | 10 γ/10 γ | 2 (10*) | 0 | 0 |
| | 25 γ/10 γ | 0 (10*) | — | — |
| 4-Aminopteroyl d (−) glutamic acid | 5 γ/20 γ | 10 | 70 | +++ |
| | 20 γ/20 γ | 10 | 60 | +++ |
| 4-Aminopteroylaspartic acid | 100 γ/5 γ | 10 | 0 | 0 |
| | 100 γ/10 γ | 10 | 20 | + |
| | 100 γ/25 γ | 9 | 33 | + |
| 4-Aminopteroylthreonine | 10 γ/10 γ | 10 | 50 | ++ |
| | 25 γ/10 γ | 10 | 20 | + |
| 4-Aminopteroyl α alanine | 10 γ/10 γ | 10 | 70 | ++ |
| | 25 γ/10 γ | 10 | 60 | ++ |
| 4-Aminopteroylserylglutamic acid | 50 γ/20 γ | 10 | 90 | +++ |
| | 100 γ/20 γ | 10 | 30 | ++ |
| | 200 γ/20 γ | 10 | 30 | + |
| | 500 γ/20 γ | 9 | 0 | 0 |
| | 1000 γ/20 γ | 6 | 0 | 0 |

* Where toxicity of compounds reduced the number of birds in the group, (*) signifies the original numbers used.

TABLE 5

THE INHIBITORY EFFECT OF OTHER RELATED COMPOUNDS ON THE ACTIVITY OF PTEROYLGLUTAMIC ACID IN GROWTH OF ROUS SARCOMA

| *Compound* | *Am't inj. daily/am't of PGA* | *Total no. of chicks* | *% chicks w. tumors* | *Avg. tumor size* |
|---|---|---|---|---|
| 9,10-Dimethylpteroylglutamic acid | 10 γ/10 γ | 10 | 20 | ++ |
| | 100 γ/10 γ | 9 | 22 | + |
| | 500 γ/10 γ | 10 | 30 | + |
| 6-Methyl-7-pteroylglutamic acid | 10 γ/10 γ | 10 | 50 | ++ |
| | 100 γ/10 γ | 9 | 77 | ++ |
| | 500 γ/10 γ | 8 | 87 | ++ |
| | 1000 γ/20 γ | 10 | 80 | +++ |
| 7-Methylpteroylglutamic acid | 10 γ/10 γ | 10 | 50 | ++ |
| | 100 γ/10 γ | 10 | 20 | + |
| | 500 γ/10 γ | 9 | 22 | + |
| 7-Carboxy-6-pteroylglutamic acid | 100 γ/20 γ | 9 | 100 | +++ |
| | 1000 γ/20 γ | 9 | 88 | +++ |
| Pteroyl (d) serylglutamic acid | 50 γ/20 γ | 7 | 28 | ++ |
| Controls | 10 | 20 | 85 | ++ |
| | 20 | 10 | 100 | +++ |

tained with 25γ of PGA. In the group receiving 0.2γ of vitamin $B_{12}$, however, the inhibitor was reversed by only 5γ of PGA. In the absence of PGA, the $B_{12}$ has no apparent effect. This experiment has been repeated with aminopterin and with 4 amino-9-methyl PGA. Similar results were obtained, using both vitamin $B_{12}$ and 15 unit liver to obtain this lowering of the inhibition index.

The most potent inhibitor is aminopterin. As little as 20γ in a single dose will kill a weanling rat in a few days. The histological changes produced by this compound are evident within 24 hours. The bone marrow, thymus, and spleen are principally affected. Other derivatives produce similar changes at high levels.

The discovery that folic acid is essential to the growth of Rous sarcoma implants in chickens makes this tumor a useful tool in studying the role of nutrition in tumor development. Vitamin $B_{12}$ has also been shown to be involved in the growth of this sarcoma.

The level of dietary protein markedly affects the growth of Rous tumor. FIGURE 1 illustrates the effect of several levels of dietary protein on the growth of the tumor in the absence of PGA and vitamin $B_{12}$. At protein levels below 30 per cent, a high incidence of tumors is obtained, while at levels of 30 per cent and over, the incidence drops to zero.

Further illustration of this is given in FIGURE 2. Chicks fed 30 per cent and 60 per cent protein require both vitamin $B_{12}$ and PGA for maximum tumor development, while at the lower levels neither factor is required. It would appear that the requirement for both of these factors is increased with a high protein intake. Such chicks were found to be more sensitive to the antagonists. On protein-free diets, the chicks develop well-defined tumors even though the birds lose considerable weight.

The inhibition of Rous sarcoma by various PGA antagonists follows the pattern of growth inhibition. TABLES 4 and 5 give some typical examples, which need no further discussion here.

Histochemical studies on Rous tumor have demonstrated the presence of many substances stainable by various techniques. Preliminary studies on the effects of 4 aminopteroylaspartic acid on the tumor showed that phosphamidase, potassium, and iron were decreased, while the cytochrome oxidase, zinc, and polysaccharide stains gave variable changes.

Several vitamins are known to affect immune responses in animals. PGA deficiency in chicks inhibits agglutinin response to *E. typhosa*, *B. abortus*, and other organisms. The administration of PGA permits a high titer to develop. TABLE 6 gives a typical example, in which the vitamin was incorporated in the vaccine. This immune response is inhibited by the deficiency or by administration of an antagonist.

TABLE 6

EFFECT OF PTEROYLGLUTAMIC ACID INCORPORATED IN THE VACCINE ON THE AGGLUTININ RESPONSE OF CHICKS TO *B. abortus**

| *Am't PGA in each dose of vaccine* | *Total am't injected* | *Total no. of chicks* | *Avg. titer of agglutinins* | *Range of agg. titers* |
|---|---|---|---|---|
| None | 0 γ | 36† | 1:3.5 | 0:1:8 |
| 5 γ | 30 γ | 7 | 1:12.5 | 1:4–1:32 |
| 20 γ | 120 γ | 8 | 1:18.0 | 1:16–1:32 |
| 50 γ | 300 γ | 11 | 1:157.0 | 1:32–1:512 |

* Day-old chicks were placed on the pteroylglutamic acid-deficient diet. On the 8th, 10th, 12th, 15th, 17th, and 19th days, doses of vaccine containing 10 billion formalin-killed *B. abortus* organisms (0.5 ml.) and pteroylglutamic acid as indicated were given by intramuscular injection and the birds were bled 6 days after the last treatment.

† Six tests.

## *Summary*

Biological studies on a number of PGA derivatives are reported. Certain interrelationships between PGA derivatives and dietary protein and vitamin $B_{12}$ have been illustrated.*

* The compounds used were prepared by chemists at the Lederle Laboratories and Calco Chemical Company. The biological experiments were done in cooperation with P. A. Little, P. K. Roesch, H. B. Ritter, B. L. Hutchings, and A. R. Whitehill. Because of space limitations, many obvious and pertinent literature references have been omitted.

## *SECTION OF PSYCHOLOGY**

### THEMATIC APPERCEPTION: FAILURES AND THE DEFENSES†

*By* LEOPOLD BELLAK‡

In speaking of thematic apperception, we will restrict ourselves to a consideration of responses to the Thematic Apperception Test (TAT), the Make A Picture Story (MAPS), the Symonds' Picture Story Test, the Children's Apperception Test (CAT), and the Four Picture Test (FPT) (with which last the author's experience is extremely limited.) Some of the observations we wish to make, however, may hold true for the broader field of projective techniques, including the Rorschach.

#### *Failures of Apperceptive Methods*

Among clinical problems which arise in the methods of personality investigation, the most obvious and clear-cut of all difficulties are the failures of apperceptive methods. The subject has found scant, if any, consideration in the literature thus far, possibly owing to the honeymoon spirit currently prevailing in clinical psychology. Nevertheless, an investigation of these failures should be very important for the basic understanding of the dynamics of these methods and their limitations.§

By failure of an apperceptive method, we refer to: (a) an apparent lack or paucity of meaningful results; and (b) results which are apparently grossly inconsistent with incontrovertible clinical facts.

(*a*) *Apparent Lack of Meaningful Results.* The most obvious extreme of this type of failure exists when a patient refuses to give any responses at all. On that continuum, we also deal with too-brief responses or those of a barren, purely descriptive nature. It is obvious that a certain amount of voluntary cooperation by the subject is indispensable: if projective techniques are compared to X rays, it is necessary that the patient at least step behind the X-ray screen. This "cooperation" lies on a continuum of a relationship between tester and subject which has been described as "rapport" and was recently discussed by Joel[2] as "the interpersonal equation in projective methods." It resembles in essence the transference-countertransference problems of the psychoanalytic session.

The test situation and the examiner himself may be apperceptively distorted by the subject (as is most clearly seen in the paranoid) and, at the same time, attitudes of the examiner may influence the situation. Joel's point is well taken, that it should be helpful to have the examiner's reaction to the subject recorded as part of every protocol. If "establishing rapport" means that one puts the subject at ease, one must be aware of one's own involuntary attitudes. At the same time, it must be remembered that overfriendliness may also cause difficulties, such as homosexual anxiety. In this context, it should be pointed out that the influence of the sex of the examiner on the test results has never been sufficiently investigated.

Having touched briefly on the more obvious problems pertaining to lack or great dearth of responses, it remains to discuss those cases where the responses are quantitatively sufficient but barren in quality. This problem is so closely related to the situation where the results are inconsistent with known facts that we will discuss it in that context.

(*b*) *Results Inconsistent With Clinical Facts.* As an example of inconsistency of TAT results, we will cite the case of a 14-year-old boy who had killed a small child, apparently in some sexual excitement. Institutionalized, he was a model inmate on a behavioral level—bland, noncommittal, and inaccessible to psychotherapy. At the time of commitment and again when he came up for disposition at the end of a year, he was given Thematic Apperception

* There was no meeting in January of the Section of Physics and Chemistry.

† This paper, illustrated, was presented at the meeting of the Section on January 16, 1950.

‡ Associate in Psychiatry, New York Medical College; Lecturer in Psychology, New York University and the New School for Social Research, New York, N. Y.

§ A detailed discussion of specific cases is planned for the future by Mr. Ernest Parkes and the author.

Tests, Rorschachs, and other tests by the staff for help in understanding his problems. When none of the tests threw any light on the psychodynamics of the crime, he was referred to me for the administration of a TAT under the influence of intravenous sodium amytal. After the intravenous administration of 7½ gr. sodium amytal and 1½ gr. nembutal orally, a marked psychomotor effect of the drugs was noted: general relaxation, drowsiness, slurring of speech, and occasionally such lack of motor control and sleepiness that the TAT cards dropped out of his hands. Despite the action of the drugs, the boy gave 15 stories, which in no single instance revealed any *primary* pathological evidence in the theme itself that would have permitted one to pick out his TAT as belonging to a noticeably disturbed person.

There are a number of such cases and similar ones. For instance, in a woman patient of 30 with severe sadomasochistic problems and extensive phobias, which were studied in detail during two years of psychoanalysis, the TAT, administered prior to the beginning of analysis, failed to show any clear evidence of the existing pathology.

Needless to say, there are a great many protocols where a good deal of seemingly pathological material appears which cannot be correlated with the factual clinical data. I am not even referring to the vogue for diagnosing nonexistent schizophrenias. It seems that projective methods often reveal potentialities rather than actualities. The question we are faced with is: Just what happens in the kind of cases cited here? How does it happen that these patients' problems fail to appear in the tests, even though we have every reason to believe that the subjects are consciously cooperating to the best of their ability? We may profit by comparing these findings with a comparable psychoanalytic situation, namely, the one of unconscious resistance and a mobilization of defenses.

*Defenses in Apperceptive Techniques*

In clinical psychoanalysis, attention was first primarily focused on the "id" drives. Later developments, outstandingly Anna Freud's book, "The Ego and the Mechanisms of Defense,"[1] revealed the personality as a delicate matrix of the defense mechanisms and led to the study of the ego. Similarly, it can be said that the id impulses, needs, and drives have so far been the center of attention in apperceptive and, possibly, all projective techniques. The time has come to make a step comparable to the one in psychoanalytic development and study apperceptive protocols specifically from the standpoint of the defenses as indicators of personality structure, as criteria of assets and liabilities, and often as the only clues to impulses which themselves may have become completely invisible.

Defenses in the TAT can be observed in the story content itself, as in the story sequence, or in the sequence of themes to the same picture. For instance, simply not seeing the gun in 3 BM or 8 BM constitutes a scotoma, a simple repression. Similarly, if a patient referred to the woman leaning against the tree in #2 as slim, thin, and well proportioned, when most other people see her as presumably pregnant, we deal with direct denial and turning into the opposite. Displacement of a story into the middle ages or onto the moon, *etc.* is a familiar mechanism.

On the other hand, if we have a story to 17BM of a circus performer who always wanted to have a solo act instead of being part of a trio, and the story progresses to where another member of the troupe has an accident in which the hero is helpful and is rewarded by a solo act, then we can formulate the following: this person wants to be in the limelight and do away with the competitors; this thought is not permitted expression. Instead of the aggressive thought, the hero gives help in an accident; that is, the aggression is impersonalized, the helpfulness appears manifestly, and the original goal is given as a reward. In other words, sequence of the story demonstrates this subject's use of reaction formation in dealing with aggression. Sometimes a picture of the entire defensive nature of the character structure reveals itself clearly in the TAT.

On the other hand, one may see particu-

larly obsessive compulsives offer several themes to one story, guarding against aggressive thoughts which nevertheless come out even in the final elaboration. However, we can differentiate patients who start with the most manifest appearance of the aggressive (or sexual) impulse and end with a most disguised theme to one picture from those patients who do it in reverse, *i.e.*, those whose first attempt at a story to a picture is the least manifest, with the impulse being permitted more and more direct expression as the patient tries to offer a different story. My assumption, so far, has been that in the first case there is still a firmer control of the forbidden impulse, which has to be interpreted in the context as either more anxiety or a relatively stronger ego.

It is clear that the response to a test situation constitutes a problem which the patient has to solve. The type of ego activity involved is fairly unique in that it is much more controlled than a nocturnal dream, involves a more defined task then the daydream, and needs freer reins than do the structured problems of everyday routine. Thus, the situation demands an ego that can perform a specific task and yet allow some relaxation of its grip on the id impulses (if such anthropomorphic language may be permitted). It must be borne in mind in this context that it is a normal function of the ego to *exclude itself*.* If this function of self-exclusion of the ego is disturbed we see such disorders as insomnia, inability to rest, and inability to perform creative tasks. In these cases, we find that a relatively weak ego is so afraid of a break-through of forbidden id impulses that it dares not relax its constant vigil. Similarly, resistance in analysis occurs when there is an increase of anxiety concerning certain thoughts which the ego defends itself against by excluding *all* thoughts. Such extremes in characterological defensiveness are clinically well known as manifestations of rigidity and lack of spontaneity.

* We are indebted for this formulation to a verbal communication by Dr. Ernst Kris.

We may now apply what we know of defensiveness in the therapeutic situation to apperceptive techniques. It becomes easily intelligible that extreme defensiveness may be the reason for barren or inconsistently innocuous protocols in clinically very distorted patients.

### *Defensive "Failures" in Relation to General Problems of Interpretation*

Rosenzweig[3] has recently pointed out that we deal with two types of frames of reference in the interpretation of apperceptive methods. The first concerns an interindividual comparison, *i.e.*, of a given subject's responses to the responses of a sample population. For instance, as in psychometric tests, we say that a large percentage of the population sees the pistol in 3 BM, and that therefore not seeing it must have a meaning. The second type of comparison we make is an intraindividual one. We study the repetitiveness of certain themes and base our interpretations on this factor. I would add to his conceptualization a third comparison as the basis of interpretation, namely, a comparison of the fantasy test behavior with the manifest personality.

With these frames of reference in mind, we can then state that, if a response is markedly different from those given by the population sample, *e.g.*, markedly more benign, we have reason to suspect it. For example, if the majority of subjects see the two figures in 18 GF as one strangling the other, and the young murderer mentioned earlier says that it is a mother consoling her daughter for having fallen downstairs, we can infer that this response is possibly motivated by his defense against his own aggression. On the other hand, if we find that a subject gives a theme of extreme aggression to a story and then changes it to a more innocuous version and later has primarily innocuous themes, we are again entitled to the inference that they are the result of defensiveness. Similarly, it is now obvious that projective protocols must be considered hand in hand with as much

clinical information as possible for a comparison and mutual evaluation of the two sets of data.

As in the psychoanalytic situation, small break-throughs of original impulses must be looked for to illuminate what it is the patient is resisting. For instance, in the stories of the young murderer, he made one slip of the tongue in his story to picture 8 BM, where he said,

> "These two boys have gone out hunting. They shot a lot of boys—I mean, animals, and decided to split up to get more pheasants. They agreed to meet at 8:30 at night to count the game and to go home. This boy was standing in the bushes. Twenty feet from him he heard something move. He goes to look at what he caught and finds his friend and rushes him to the doctor. The doctor says the boy will be all right and in the end the boy gets O.K. and forgives him for what he did."

The slip betrays the apparently original aggressive impulse which becomes absorbed in a perfectly acceptable hunting story, then breaks through again in the boy's injury. An inquiry into the small detail of 8:30 at night revealed that that was the time for lights out at the institution and strongly suggested that it is at this time that his fantasies are permitted to emerge. Similarly, he started his story to picture 1 like this:

> "This boy does not like to practise his trumpet—I mean he likes to play his violin."

He changes a negative response immediately to a positive one. The story he gives to picture 15 is as follows:

> "An undertaker; he is very sad because he is putting to rest all these people. He goes out one night and looks with remorse at all the work he has done. He tries to find out how he can undo his work. He can do nothing about it."

In this story, the undertaker behaves as if he had killed all the people he buried, revealing the original aggressive impulse only by what would otherwise be incongruent guilt feelings.

One must also make note of negations in TAT stories; that is, when a subject says that the hero is *not* angry, it presupposes that the first thought was that he *is* angry, and that the negation is defensive. Freud stated that such thoughts can best be translated "I wished he were not angry." By using such methods then, we trust that what may at first glance appear as barren and unrevealing stories, constituting failures of apperceptive techniques, may be turned into significant information, particularly concerning defenses.

To avoid barren records, sedation is usually more helpful, in my experience, than in the case of the young murderer. Either intravenous sodium amytal or oral sedation by fast-acting barbiturates are frequently effective means of decreasing the defensiveness in subjects in whom previous tests were relatively uninformative or in whom one has reason to expect unusually great conscious and unconscious resistance. The barbiturates presumably decrease the anxiety, and thus the need for defensiveness, and at the same time decrease the ego strength.

Another possible approach to avoiding relatively uninformative records is suggested by a recent experiment by Stein[4] on the effect of time pressure on Rorschach results. He exposed Rorschach cards tachistoscopically, at four different speeds, and found an increasingly clearer revelation of the "deeper" problems, less and less disguised by defenses. One might draw the inference from this experiment that in certain subjects, where one need not worry too much about the deleterious effect of additional anxiety, a time limit on apperceptive performances may produce better results. The anxiety may be so increased that the defenses break down. On the other hand, in some patients, this may lead to further tightening up and complete refusal of responses.

### *Summary*

Failures of apperceptive techniques, as one problem clinicians face, have to be understood in terms of defensiveness against anxiety, as in the psychoanalytic situation.

A study of secondary features of the protocol may reveal the nature of the defenses, and indirectly the warded-off impulses. Pre-test sedation and time limits for responses may be two means of avoiding relative lack of information by decreasing anxiety or ego strength in turn.*

* After presentation of the paper, the author received a paper by Dr. Silvan S. Tomkins, "The present status of the thematic apperception test" (from the *American Journal of Orthopsychiatry*, Vol. XIX, No. 2, April 1949), which also deals with the problem of failures with the TAT.

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## *SECTION OF ANTHROPOLOGY*

### THE MEXICAN CALENDAR AND THE FOUNDING OF TENOCHTITLAN-TLATELOLCO†

*By* PAUL KIRCHHOFF‡

Mesoamerica is the only part of pre-Columbian America where an advanced calendar and pictorial writing created the basis for the keeping of historical records. In this region, therefore, and in this region alone, can the study of the archaeological remains be supplemented by the study of native annals, thus creating a situation similar to that found in many parts of the Old World. The combination of these two types of research should give us a much better knowledge of the actual course of events in this part of pre-Columbian America than we have now, and, based on this better knowledge, a better understanding of historical processes and forces involved than we may hope to attain in any other part of America.

One of the most important and interesting social phenomena in Mesoamerica, paralleled in the New World only in the Andean civilizations, is the city. The history of Mexico City is unique in that it is the only well-documented history of a pre-Columbian city anywhere on this continent covering a period of considerable length. This history, which has not yet been studied properly, contains a great wealth of important data, among them the dates when certain public buildings (pyramids, temples, and aquaeducts) were started and finished.

As a preliminary report on an investigation still in progress, I have selected for analysis one single moment in the history of Mexico City, that of the founding of the twin cities, Tenochtitlan and Tlatelolco, of which it consisted. Out of the many interesting aspects of this event that could be studied, I have selected the one that may seem the most arid but which actually is the indispensable basis and starting point for the study of all other phases, as well as for the study of the subsequent history of Mexico City, namely, the chronological aspect. The exact date of the founding of Tenochtitlan and Tlatelolco is important above all because we want to know how long it took to build the city the Spaniards found and described. This will be of importance not only for the history of Mexico City itself, but also because it will provide us with a comparative yardstick for the study of the archaeological remains of other cities for which no written records exist and, at the same time, for our comprehension of the nature of Mesoamerican cities and of Mesoamerican society as a whole.

† This paper was presented at the meeting of the Section on January 23, 1950. The research for this paper was supported by a grant-in-aid from the Viking Fund, Inc.
‡ Department of Anthropology, University of Washington, Seattle, Washington.

For that part of Mesoamerica with which we are here concerned (the Valley of Mexico and surrounding regions), the principal features of the calendar serving as a basis for dated recordings may be summarized as follows. Every day and every year has a name, composed of a number (1–13) and a sign (20 in the case of day names, but only 4, called year bearers, in the case of year names). The resultant combinations of numerals and signs are 260 in the case of day names and 52 in the case of year names. After 260 days and after 52 years, new day and year cycles start, with day names and year names identical with those of the preceding periods.

In the original sources, lost today, events seem to have been recorded either under a year name only or under a year name and a day name. The secondary sources known at the present time, whether pictorial or written, contain very few day dates, a minute fraction of the great number of year dates recorded. Sources written in the Nahuatl language give their dates in terms of the native calendar, and fortunately some of the sources written in a European language do the same. Others, however, give only the equivalent dates in our own calendar. Thus, the only day date referring to the founding of Mexico City, recorded by Sigüenza y Gongora in the 17th century, on the basis of a pictorial history since lost, is given only in terms of our calendar—July 18. The day date 1 Crocodile, recorded in the "Anales de Tlatelolco," seems to refer to a somewhat later moment, namely, the inauguration of the first, still very simple, pyramid in Tenochtitlan.

The retranslation of dates given only in terms of our calendar into the native calendar, on the assumption that the most common correlation, 1519 = 1 Reed, was used, has proved feasible and useful in other cases. We have refrained, however, from the inclusion of such retranslated dates in our analysis of the dates given for the founding of Mexico City.

TABLE 1 lists all known native dates for the founding of either Tenochtitlan or

TABLE 1

| *Dates* | | *Founding of* | *Sources* |
|---|---|---|---|
| (1) 1 Rabbit | = | 1194: Tenochtitlan | Codex Xolotl, Alva Ixtlilxochitl |
| *cf.* 1 Rabbit | = | 1246: conflict with Colhua; the Mexicans leave Colhuacan | Anales de Quauhtitlan |
| (2) 2 House | = | 1273: Tlalcocomocco (Tenochtitlan) | Anales de Quauhtitlan |
| (3) 8 Rabbit | = | 1318: Tenochtitlan | Anales de Quauhtitlan (Duran says only: "1318") |
| (4) 2 House | = 1324 | 1325: Tenochtitlan, Tlatelolco | (Tenochtitlan, 1324:) Codex Mendoza, Mendieta, *etc.*; (Tenochtitlan, 1325:) Anales de Tlatelolco, Chimalpahin, *etc.*; (Tlatelolco, 1325:) Veytia |
| (5) 3 Rabbit | = | 1326: Tenochtitlan | Tezozomoc, according to Veytia (doubtful)* |
| (6) 4 Reed | = | 1327: Tenochtitlan, Tlatelolco | (Tenochtitlan and Tlatelolco:) Tablas cronologicas in Boturini-Veytia's "Texcoco en los ultimos teimpos"; (Tenochtitlan:) Sigüenza, and authors following him |
| (7) 9 Knife | = 1331† | : Tenochtitlan | Ventura Zapata, according to Veytia |
| (8) 1 House | = | 1337: Tlatelolco | Anales de Tlatelolco, Chimalpahin, *etc.* |
| (9) 2 Rabbit | = | 1338: Tlatelolco | Clavigero |
| (10) 2 Knife | = | 1364: Tenochtitlan | Codex Aubin |
| (11) 4 Rabbit | = | 1366: Tenochtitlan | Codex Vaticanus A, Mappe de Tepechpan |

* The inclusion of this date is based only on the statement by Veytia that "Alvarado Tezozomoc gives to understand that the year was 3 Rabbit, which could refer to the year 1326." No such reference can be found in Tezozomoc's published writings, but it is quite possible that Veytia used another manuscript of Tezozomoc's that has been lost since.

† Veytia's "1321" is clearly a misprint, as the context shows.

Tlatelolco, the twin cities founded by the Mexicans, and the years of our calendar with which these native years have been equated by our sources, explicitly or implicitly. Equations based on the correlation 1519 = 1 Reed have been entered in the second column, those based on the less frequent, but by no means uncommon, correlation 1518 = 1 Reed (*i.e.*, 1519 = 2 Knife), in the first.

It is often said that the difficulty with Central Mexican annals is that there is no way of distinguishing the years of the same name in different 52-year cycles. This is obviously not the source of our difficulty in this case, as it is in all but a few others. Only one date, that of 2 House, occurs twice in our list. A much greater difficulty lies in the curious fact that, whereas all other equations. These changes result in the reformed TABLE 2, in which, for simplicity's sake, we have also converted all equations based on the correlation 1 Reed = 1518 into those based on 1 Reed = 1519. This is the chart which will be used in the following analysis.

TABLE 2

| | | | |
|---|---|---|---|
| (1) | 8 Rabbit | =1318: Tenochtitlan | |
| (2) | 2 House | =1325: Tenochtitlan, | Tlatelolco |
| (3) | 3 Rabbit | =1326: Tenochtitlan | |
| (4) | 4 Reed | =1327: Tenochtitlan, | Tlatelolco |
| (5) | 9 Knife | =1332: Tenochtitlan | |
| (6) | 1 House | =1337: | Tlatelolco |
| (7) | 2 Rabbit | =1338: | Tlatelolco |
| (8) | 1 Rabbit | =1350: Tenochtitlan | |
| (9) | 2 Knife | =1364: Tenochtitlan | |
| (10) | 4 Rabbit | =1366: Tenochtitlan | |

other dates are given for the founding of either Tenochtitlan or Tlatelolco, 2 House and 4 Reed are given for both. Taking this into consideration, we are faced, then, with eight different native dates for Tenochtitlan (counting the two 2 House dates as only one) and four for Tlatelolco. Some of the dates for Tenochtitlan precede those for Tlatelolco, while others follow them.

The first two equations with years of our calendar are undoubtedly far too early. Mexico City was certainly founded sometime in the fourteenth century. By adding a full 52-year cycle to the second date in our list (*i.e.*, the first 2 House date), we arrive at the year 1325, the year with which the second 2 House date has been identified by other sources; and by adding three complete 52-year cycles to the first date in our list, we arrive at another 1 Rabbit date, namely, 1350, which seems more in line with the

While we have now reduced the total time span, in terms of equations with our calendar, from 172 years to 48 years, we are still confronted with essentially the same conflict between a great number of dates, and of years over which they spread, and the clear indications in all our sources, sometimes explicit, sometimes implicit, that the founding of both Tenochtitlan and Tlatelolco were events which took place in specific years, and in those years alone. We might, in spite of this, feel inclined to interpret the repeated spreading of dates over a short number of consecutive years (for Tenochtitlan, twice over three years, and for Tlatelolco, once over three years and once over two years), as indicating, after all, a slow settlement that spread over a number of years, if it were not for the fact that for each city there are *two* such blocks of years. Besides, we find the same spread over as many as four consecutive years (though never more) to be characteristic of all kinds of events, including those which, like coronation ceremonies or solar eclipses, took place on a specific day. These regular differences, not fully understood at the present time, may be connected with different year beginnings, possibly each of them characteristic of one of the four quarters into which so many Mesoamerican cities were divided.

More striking is the great number of dates that are widely separated. In view of the obvious impossibility of reconciling them, so long as modern students have accepted the tacit assumption of sixteenth century writers that all these dates belong to one single year count, and in view of the equal impossibility of accepting all of them, the only feasible, though very unsatisfactory, procedure seemed to be to select one,

or rather two, as "the most acceptable." Most modern authors have selected the date 2 House = 1325 for the founding of Tenochtitlan, and the date 1 House = 1337 (*i.e.*, 12 years later) for the founding of Tlatelolco; and this in spite of the fact that several sources definitely state, or at least imply, that not Tenochtitlan but Tlatelolco was founded first.

The division of the Mexicans into two sections, which settled apart and started independent histories with opposite foreign orientations—Tenochtitlan towards Colhuacan, and Tlatelolco towards Azcapotzalco (see FIGURE 1)—is an event of first-rate significance, and it would be important to be able to decide whether there was for a number of years a common settlement from which, several years later, one group split away, or whether the two groups started separate settlements from the very beginning, as Boturini and the author of the "Historia de los mexicanos por sus pinturas" seem to imply. It is significant in this respect that Veytia, according to whom the founding of Tlatelolco preceded that of Tenochtitlan by two years, gives the date 2 House, usually connected with Tenochtitlan, for the founding of Tlatelolco.

Recent research has led to discoveries which make possible a new approach to our problem. It has been established that 13 different year counts existed in the area from the Mesa Central to Northern Oaxaca. This number includes the year count which for a long time had been considered to be the only one used in that area, *i.e.*, the year count of Mexico City, in which the year 1519 was called 1 Reed; the Mixtec-Popoloca year count discovered by Jimenez Moreno, in which that year was called 13 Reed; and the Matlatzinca year count established by Caso, in which it was called 3 Reed. The additional ten year counts that have been discovered since follow the same pattern. In each of them, the same year has the same year bearer but a different numeral. With 13 numerals used, 13 different year counts are possible, and all of them are found to have actually been in use.*

The utilization of the 13 year count correlation in the analysis of apparently conflicting dates for a given event has opened up new avenues of research. No longer do we have to select from several dates one as "the most acceptable." Every one of them turns out to be correct, though only within a given year count used by a particular people or in a particular city. Far from leaving us in a state of bewilderment, as

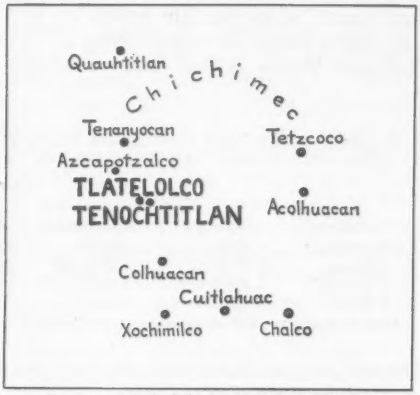


FIGURE 1. Principal cities in the Valley of Mexico

before, these apparently conflicting, but in reality parallel, dates now help us to place an event with an accuracy that increases with each additional date that we discover in our sources.

This is as true of the many dates reported for the founding of Mexico City as it is of all other dates that we have analyzed in the course of our investigations. The 13 year count correlation, however, has not been worked out on the basis of the analysis of such individual events. It is based rather on analysis of coupled events, for which several sources give different dates but equal intervals, and on specific statements in our sources to the effect that certain dates be-

* The spread of dates referring to a single event, over up to four consecutive years, seems to occur in several, and possibly all, of the 13 year counts. This suggests the possibility that each of them had several variants, sometimes, if not always, four in number.

long to the historical records of certain peoples or cities. Our dates for the founding of Mexico City are unsatisfactory in both respects. The situation is especially difficult, as well as intriguing, because practically all of our sources switch from one year count to another, at the time of the founding of Mexico City or of one or both of the important events preceding or following it: the arrival and defeat in Chapoltepec, and the crowning of the first two kings of the newly founded twin cities. It is apparent already that these shifts from one year count to another are related to realignments among the peoples living in the Valley of Mexico at that time. To date, however, only the barest beginning has been made along this line of analysis.

Applying the 13 year count correlation (segments of which are shown in TABLE 2) to the dates referring to the founding of Mexico City, we find that all of them (*i.e.*, both those reported for Tenochtitlan and those for Tlatelolco) correspond to the same year, or rather to a group of four consecutive years (see above). Tenochtitlan and Tlatelolco must have been founded in the course of the same year, and not 12 years apart.

Our dates for the founding of Tenochtitlan come from five different year counts: those of Mexico City itself, Colhuacan, Cuitlahuac, the Chichimec of Tenanyocan-Tetzcoco-Quauhtitlan (all in the Valley of Mexico—see FIGURE 1), and either Huexotzinco or Tlaxcallan (in the Valley of Puebla). The dates for the founding of Tlatelolco come from only two year counts: again, that of Cuitlahuac, and that of the Tepanec of Azcapotzalco.

While not too much significance should be attached to the fact that dates for this event are not available in all of the year counts of the nearest neighbors of the newly settled Mexicans, it is certainly striking and suggestive that dates from Colhuacan (*i.e.*, the city that gave Tenochtitlan its first king) are known only for Tenochtitlan, and dates from Azcapotzalco, the city that gave Tlatelolco its first king, for Tlatelolco alone. On the other hand, two dates from the Cuitlahuac count are reported for the founding of both Tenochtitlan and Tlatelolco. What is still more striking, precisely those sources that give an Azcapotzalco date for the founding of Tlatelolco, give for the founding of Tenochtitlan not a Colhuacan but a Cuitlahuac date, namely, the year 2 House. Similarly, Chimalpahin, an author from Chalco who uses the Chalco year count for the earlier history of his city, uses the Cuitlahuac, not the Mexico City year count, for the earlier history of the Mexicans, including the Cuitlahuac date 2 House for the founding of Tenochtitlan. Another example is the "Histoyre du Mechique," a source based largely on the tradition of Acolhuacan, which likewise gives this Cuitlahuac date, although interestingly enough it equates it with the Christian year 1321 (instead of the usual 1325), which shows that its author used an Acolhuacan correlation chart.

As a matter of fact, the Cuitlahuac date for the founding of Tenochtitlan (and similarly, the earlier Cuitlahuac date for the defeat in Chapoltepec) seem to have been

TABLE 3

SEGMENTS OF SIX YEAR COUNTS INTO WHICH FIT THE DATES REPORTED FOR THE FOUNDING OF TENOCHTITLAN AND TLATELOLCO, AND THE CHRISTIAN YEARS TO WHICH THEY CORRESPOND

| | | *Year counts of* | | | | |
|---|---|---|---|---|---|---|
| *Colhuacan* | *Cuitlahuac* | *Azcapotzalco* | *Chichimec* | *Huexotzinco? Tlaxcallan?* | *Mexico City* | *A.D.* |
| 2 KNIFE* | 1 Knife | 13 Knife | 12 Knife | 9 KNIFE | 6 Knife | 1368 |
| 3 House | 2 HOUSE | 1 HOUSE | 13 House | 10 House | 7 House | 1369 |
| 4 RABBIT | 3 RABBIT | 2 RABBIT | 1 RABBIT | 11 Rabbit | 8 RABBIT | 1370 |
| 5 Reed | 4 REED | 3 Reed | 2 Reed | 12 Reed | 9 Reed | 1371 |

* Capital letters are used for those year names for which this event has been reported.

considered by one Mexican tradition, represented by several important sources, as actually belonging to the year count of Mexico City, just as the Azcapotzalco date for the founding of Tlatelolco. It is not clear yet what gave the city of Cuitlahuac, or "Little Venice" as it was called by the Spaniards, such an outstanding place in the history of the people who settled in Mexico City; but the general importance of that city, scarcely ever mentioned by modern students, is beyond any doubt. The importance of Cuitlahuac dates for the founding of Tenochtitlan is further underlined by the fact that the only two day dates known today likewise come from the Cuitlahuac calendar.

Only one of the dates for the founding of Tenochtitlan, namely, 8 Rabbit, comes from the year count of Mexico City, and interestingly enough it is reported by only one source and with but the merest mention of the event, without any of the usual details, "This is the year in which Mexico-Tenochtitlan started."

The date 9 knife, reported by a Tlaxcaltecan source, belongs to a year count which we have tentatively identified with either Huexotzinco or Tlaxcallan. The date 1 Rabbit, given in the "Codex Xolotl" and by Alva Ixtilxochitl, both Tetzcocan sources, belongs to the year count that was used by the Chichimec of Tenanyocan-Tetzcoco-Quauhtitlan. The anonymous author of the "Anales de Quauhtitlan," who explicitly states that he makes use of the annals of several peoples or cities, with conflicting dates, reports for a year 1 Rabbit a fight between the Colhua and the Mexicans and the withdrawal of the latter. The context makes it clear that this is the battle that took place at the time the Mexicans abandoned Colhuacan, where they had lived in vassalage and from where they proceeded to settle in Tenochtitlan and Tlatelolco. Our source reports this fight in a section which begins with the words "This is the story of the old men of Quauhtitlan," and this date actually belongs to the year count which we have been able to identify with the Chichimec of Quauhtitlan, as well as of Tenanyocan-Tetzcoco.

Actually, the "Anales de Quauhtitlan" gives three different dates for the founding of Mexico: (1) the date 1 Rabbit, equated with the year 1246, for the Mexicans' battle with the Colhua and their departure from Colhuacan; (2) the date 2 House, equated with the year 1273, for their settling in "Tlalcocomocco," which is only another name for the locality where Tenochtitlan was founded; and (3) 8 Rabbit, equated with the year 1318, for the "beginning in Mexico-Tenochtitlan." Since the author of the "Anales de Quauhtitlan" did not realize that these are three parallel and synchronous dates, belonging to different year counts, he erroneously accommodated them all in one count. As a result, his whole chronology was hopelessly thrown out of gear and tremendously lengthened.

Since out of the total number of ten dates only one, 8 Rabbit, belongs to the year count in which 1 Reed corresponded to the year 1519, it is obvious that we have to disregard all other proposed equations with years of our calendar, as well as all statements in our sources as to the number of years by which the founding of Tenochtitlan is said to have preceded the crowning of its first king (statements that vary all the way from 10 years, in the "Mappe de Tepechpan," to 104 years, in the "Relacion de la Genealogia *etc.*"). The equation of the date 8 Rabbit with the year 1318 is, however, likewise unacceptable, since it would leave us with a full 52-year cycle for which nothing whatsoever is reported (and this immediately after and before years which are known to have been crowded with events) and since in addition it would oblige us to add 52 years to the lives and reigns of individuals who, like king Tezozomoc, are mentioned both before and after this date. We therefore equate the date 8 Rabbit not with the year 1318 but with 1370, that is, a full 52-year cycle later.

On the basis of the 13 year count correlation chart, this equation gives us the correct equations of all other dates analyzed here. They correspond to the years 1368, 1369,

1370, and 1371. As long as this four-year spread, characteristic of so many dates, is not fully understood, we propose to select provisionally the two middle years, and consider 1369 to 1370 as the date on which both Tenochtitlan and Tlatelolco were founded.

This gives us a total time span of 150 years for the history of Mexico City from its beginning to the coming of the Spaniards, as against almost 200 years, on the basis of the traditional date of 1325 for the founding of Tenochtitlan.

## *DIVISION OF MYCOLOGY*

### THE RELATIONSHIP OF *IN VITRO* TESTS OF ANTIFUNGAL SUBSTANCES TO THERAPEUTIC PROBLEMS*

*By* KURT A. OSTER AND MILTON J. GOLDEN†

An enumeration of the therapeutic problems encountered in the treatment of tinea pedis shows them to be basically the same as those met in any infectious disease. They range from prevention of the spread of infection as a general health measure to the treatment of the individual case, from the problem of carriers to the question of individual hypersusceptibility to the causative organisms. The status of the actual therapy of these tinea pedis infections is still unsettled. Eradication of the infection is the claim of a multitude of recommended preparations.

A perusal of the various textbooks of dermatology brings forth the almost uniformly expressed opinion that dermatophytosis should not be treated with strong fungicides. The recommendations for therapy vary considerably, but, either by implication or by direct mention, the use of strong fungicides is a therapeutic taboo.

This report challenges such a statement. The supporting data have been derived in the greater part from *in vitro* studies of antifungal substances and only to a minor degree from clinical observations. This procedure, unusual in that the reverse is generally the case, led to the use of the rather ambitious title of this paper.

*Theoretical Considerations.* It is common usage in the treatment of any infectious disease (and dermatophytosis does fall into this classification) to give at the start of the diagnosed or presumed infection the proper chemotherapy, proper as far as choice of the drug and its dosage are concerned. Neglect of this maxim would lead to dire consequences. Spread of the infection to the surrounding tissues or to the blood stream, chronicity of the infection, and dormancy of the invading organisms, with later recurrences and eventual possible resistance of the organisms to the therapy, might be the disastrous results. Taking into consideration these well-established principles of treatment of infections by powerful drugs, the sentence in the textbooks should then read, "Dermatophytosis should be treated with strong fungicides, if we have them at our disposal." Unfortunately, there is available not one compound which can be rightfully classified as a strong (*i.e.*, effective and powerful) fungicide.

*Definition of a Fungicide.* This statement introduces a highly confusing controversy as to the definition of the term "fungicide." Most compounds used at present in the therapy of dermatophytosis are either keratolytic or fungistatic in their actions, but not fungicidal. Hopkins and collaborators, in their extensive clinical study, came to a similar conclusion.[1] An ideal fungicide is a compound which kills fungi in every stage of growth *in vitro* and *in vivo* on short contact and in relatively low concentrations without causing damage to

* This paper, No. VII of a series entitled "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds" and illustrated with lantern slides, was presented at the Meeting of the Division on January 27, 1950.

† Research Laboratories, McKesson and Robbins, Bridgeport, Connecticut.

the host during and subsequent to its therapeutic performance. To determine a compound to be a fungicide, one needs a proper fungicidal test designed to give this information exclusively and unequivocally. *In vitro* studies must pioneer its testing, since *in vivo* tests have not been extremely reliable thus far. Demonstrations on infected humans should follow to establish the clinical effectiveness and possible eventual skin toxicity of the drug on trial.

*Fungicidal Testing.* Compounds often test wonderfully *in vitro* but show very little or no effect *in vivo*. The only lesson one should draw from this statement is that the *in vitro* tests were not properly designed to encompass the difficulties encountered in practical application. The fault lies with the tester and with the test, never with the test substance. Disregarding unknown personal sensitivities, the trichophytons grow on dead and macerated skin exclusively and therefore constitute an almost ideal example for chemotherapeutic endeavor, since healing here is the sole responsibility of the therapeutic substance. The body's own defense mechanisms, antibody formation, phagocytosis, *etc.*, would not come into play here as it does in combatting many bacterial infections.

Considering that eradication of the infection is almost solely a function of the fungicidal substance, a proper fungicidal test should also supply the answer to the question of the correct concentration of the chemical to be used in actual therapy. Most so-called "fungicidal" tests fall far short of this quality. The fungicidal dilutions of the test and the therapeutic concentrations in actual use differ frequently in multiples as high as a thousand times. By employing a functionally designed fungicidal test, it was possible to demonstrate the relative weakness of ten of the most frequently used antifungal substances.[2] This test was modified to determine also the fungicidal properties of antifungal ointments.[3] Most of these were also found to be either only fungistatic or possessing only extremely weak fungicidal properties. Use of this test method greatly diminished the discrepancies between *in vivo* and *in vitro* performances. The test is a manifestation of the relationship between a controlled contact time of fungus and toxicant, established by a suitable washing step, and the concentration of the drug. In this way, the first part of the challenge to the rule "Do not use strong fungicides" is brought out; we do not have any, as has been shown by these tests. Those substances which claim to be strong fungicides are really weak in performance and must therefore be used in high concentrations, which in turn might be irritating to the skin. Similar ideas have been brought out by Robinson for *Microsporon audouini*.[4]

*Development of Cross Resistance.* It is a commonly known fact that when bacterial infections are treated with suboptimal doses the invading organisms may develop a resistance to the drug in question. The infection must then be treated with far greater amounts of the chemical or it will no longer respond to the same substance, the organisms having become drug fast. The time element under which this bacterial resistance is developed is of major importance in therapeutic considerations. Furthermore, the organisms may or may not develop a resistance to similar therapeutic compounds chemically related or unrelated to the drug causing the resistance in the first place.

Application of this knowledge to the treatment of dermatophytosis is thus far deplorably lacking, as a survey of the pertinent literature will convince an interested investigator. Murphy and Rothman have reported that they succeeded in developing a strain of *T. mentagrophytes* with a sevenfold resistance to pelargonic acid.[5] It took them close to two years to obtain this particular strain, a period admittedly too long to be considered of importance in practical therapy of dermatophytosis. On the other hand, if it could be demonstrated that a measurable resistance of the fungi would develop to subfungistatic dosages of antifungal compounds in the relatively short

period of one week, such findings would have a definite bearing on therapeutic problems and would constitute a second challenge to the statement, "Do not treat fungus infections with strong fungicides."

By growing *T. mentagrophytes* (640 Emmons) in the presence of undecylenic acid diluted 1:35,000 and 8-hydroxyquinoline benzoate 1:90,000 for one week only, in Sabouraud's maltose broth adjusted to a *p*H of 5.7, a definite increase in resistance could be demonstrated (TABLE 1). This

TABLE 1

DEVELOPMENT OF CROSS RESISTANCE OF A FUNGUS CULTURE FOR UNDECYLENIC ACID AND 8, HYDROXYQUINOLINE BENZOATE AFTER PRE-TREATMENT WITH EITHER ONE OF THESE COMPOUNDS

| | *Original culture* | *Culture A* undecylenic acid treated* | *Culture B* 8, hydroxy-quinoline treated* |
|---|---|---|---|
| Undecylenic acid dilutions: | | | |
| 1:17500..... | + | + | + |
| 1:15000..... | − | + | + |
| 1:12500..... | − | + | + |
| 1:10000..... | − | − | − |
| 8, hydroxy-quinoline dilutions | | | |
| 1:90000..... | + | + | + |
| 1:70000..... | − | + | + |
| 1:50000..... | − | + | + |
| 1:25000..... | − | − | − |

+ growth, − no growth.
* *T. mentagrophytes* (No. 640 Emmons) grown for one week in broth containing: A. Undecylenic acid dilution 1:35000; B. 8, hydroxyquinoline dilution 1:90000.

increase in resistance was found by incorporation of the chemical into Sabouraud's maltose agar in various concentrations with subsequent streaking of the plates with the pretreated strain, which was kept growing as a stock culture on solid untreated agar and used after a period of 15 days. Using both strains interchangeably, it could be shown that a cross resistance* developed, as it was tentatively termed, of the trichophytons to a phenolic compound after exposure to a fatty acid on one hand and to a fatty acid after exposure to a phenolic compound on the other hand. These results are of only a preliminary nature at present. An investigation of the resistance behavior of the fungi to several other antifungal substances is under way, but the preliminary results appeared of such importance that they are included in this report dealing with the relationship of *in vitro* studies to therapeutic problems. It may be permissible at this point to speculate about the therapeutic significance of this finding.

By treating fungus infections with weak antifungal substances, frequently in suboptimal doses to avoid so-called "irritation," one might cause a resistance to the chemical in question to be developed by the infecting organisms. This resistance might then necessitate the use of larger concentrations of the antifungal substance to overcome the infection. If these prove unsuccessful or too irritating, an acute infection may then turn into a chronic one. (Unfortunately a multitude of tinea pedis cases are of a chronic nature.) At this point, the hypothesis is ventured that many chronic cases are the result of the insufficient treatment given at the beginning of the disease, due to the fact that the drugs used are either too weak or are used in suboptimal doses. Rothman, in his hypothesis about specificity of fungus infections of various body regions, sets up 3 points which would prove the validity of his postulation for tinea pedis.[6]

To prove the validity of the idea that fungi would develop a resistance in a short time when treated with suboptimal doses of antifungal substances not only *in vitro* but also *in vivo*, an additional point besides those mentioned by Rothman should be included. Fungi cultured from foot lesions before treatment should show less resistance to the antifungal substance used in the treatment than fungi taken from the same lesions after a short period of treatment. Experiments to examine this effect are in progress. That a positive answer to this question might be obtained seems to be indicated by the different courses of healing which a chronic fungus infection may take when treated with a rather weak and with a rather strong fungicidal substance.

* Resistance in this paper is used only in the meaning of larger demands of substances in the test to accomplish fungistasis and does not imply, for the time being, the development of resistant strains or mutations.

*The Course of Healing.* The healing of tinea pedis infection is usually accompanied by considerable shedding of skin. Keratolytics are frequently used to promote this process. The so-called "soothing" applications for the treatment of the irritated skin will not be considered in this report, since they serve a different purpose. The antifungal substances are applied then for the actual eradication of the fungus infection. The present multitude of products and the variety of their concentrations and combinations of ingredients makes one wonder about their acclaimed effectiveness. Will they actually eliminate the last vestiges of the infection, or will they give only a patched-up performance by driving the infection underground into a quiescent state? The latter possibility would explain the frequent recurrences one encounters at seasonal intervals with chronic dermatophytosis. It would be a strange coincidence indeed that the so-called "reinfections" appear on the exact site of the original infection (*e.g.*, the plantar fold of the fifth metatarsophalangeal joint) and not in a new area. One would have to ascribe to the infecting fungi a precise aiming power or to the infected area a hypersusceptibility. Neither assumption sounds credible.

A more plausible explanation of the recurrence of fungus infections at their original locations would be the fact, so emphasized in this report, that the antifungal substances employed were simply too weak to eradicate the infection completely. At the advent of favorable growth conditions, the invaders started to multiply and to cause again a manifest infection. Most cases of so-called "reinfection" could then be classified as recurrences. The blame should not be placed on the usually innocent socks and shoes, but rather on the weak therapeutic compound. A scheme is presented in FIGURE 1 which attempts to describe roughly the differences encountered in the healing process with the use of a fungistatic substance and with an ideal fungicide.

It is assumed that there is a manifest infection present at the plantar fold of the fourth metatarsophalangeal joint caused by fungi producing a pathologic host-parasite reaction, surrounded by fungi existing only as parasites without causing an inflammatory state. The same condition could also be present at a plantar area near the instep of the sole (FIGURE 1 (1)). Treatment with a fungistatic compound would transfer the active fungi into an inactive state with subsequent disappearance of the host reaction and apparent healing, but with sufficient numbers of fungi left in a quiescent state

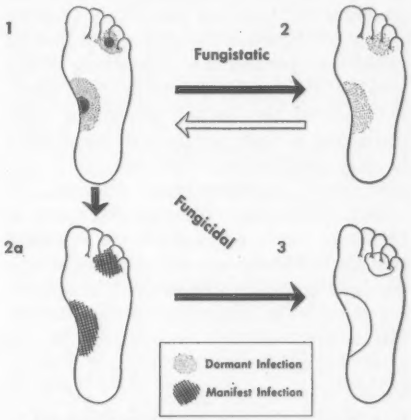


FIGURE 1. Scheme of healing of tinea pedis with fungistatic and fungicidal agents.

to cause a recurrence at the identical location, if and when favorable growth conditions reoccur (FIGURE 1 (2)). The infection then is merely subdued, and, provided the fungistatic compound is not a primary irritant or skin sensitizer, little if any irritation would be noticeable, excepting some desquamation of the infected skin.

Quite a different healing process would be encountered with a truly fungicidal substance. Its inherent effectiveness would activate or, if one may use the term, "irritate" the parasitic or dormant sites of infection. As a concentrated tuberculin injection may activate dormant foci, so the toxins of the killed fungi may activate dormant areas of fungus infection, which were not previously visible to the observer as

active lesions (FIGURE 1 (2a)). A spurious spread of the infection might then be noted, giving in some cases the erroneous impression of a primary irritation by the fungicide itself. In many clinical reports this expression of irritation is presented but not defined or explained. In the same reports, there is usually no mention made of the number of relapses encountered after clinical clearing with fungistatic compounds. After the apparent spread of the fungus infection to other areas primarily not involved, the ideal fungicide would then eradicate the infection completely (FIGURE 1 (3)). Relapses in this case would then be called true reinfections. Spreading of the skin lesion may then be considered an essential part of the healing process of tinea pedis, just as there are more or less definite healing patterns for other infections, *e.g.*, pneumonia, exanthematous diseases, *etc.*

One of the most insistent objections to the use of strong fungicides is the argument that the sudden release of fungus toxins may precipitate or aggravate severe trichophytid reactions. The similarity of the Jarisch-Herxheimer reaction encountered in the treatment of lues to the occurrence of severe trichophytid reactions in tinea pedis is quoted as a realistic deterrent to the use of strong fungicides. It might be stated here, however, that the knowledge of the possible occurrence of this reaction in syphilis therapy when involving the coronary ostia, even with eventual fatal results, has not been and will not be a deterrent to the use of the chemotherapeutic drugs employed in the cure of this disease. The trichophytid reactions encountered in the treatment of tinea pedis may range from annoying to severe. One can express reasonable doubt that they will ever be fatal. Their incidence is not of such scope that they should constitute a serious objection to the use of an effective fungicide. Furthermore, with sound clinical judgment, the fungicide may always be diluted in such a way as to prevent the occurrence of too stormy a trichophytid reaction, if suspicion of such a happening might be aroused. This procedure is utilized with the arsenicals or penicillin in the treatment of lues. The occasional occurrence of trichophytid reactions of more serious nature should then constitute no objection to the use of a strong fungicide in tinea pedis therapy.

*Conclusions.* Dermatophytosis constitutes an infectious disease and should be treated according to the same principles governing the established treatment of other infections. These would include the use of strong and effective fungicidal substances, if these are available. Neglect of these therapeutic ideas may lead to the development of resistant fungus strains and to chronicity of the infection. These suggestions are in sharp contrast with the prevailing concepts of antifungal therapy.

*Summary.* The statement that dermatophytosis should not be treated with strong fungicides is challenged because of findings obtained for the most part from *in vitro* studies. Firstly, antifungal substances used in current therapy are merely fungistatic, but not fungicidal. Secondly, the fungi may develop a resistance to suboptimal dosages of fungistatic substances. The general principle of treating an infection with optimal doses of a powerful therapeutic substance is violated when treating fungus infections with subeffective substances.

A different healing process is predicted by treating tinea pedis with an ideal fungicide. A spurious spread of the skin lesions may appear, resulting from the activation of quiescent foci of infection by toxins from killed fungi.

Trichophytid reactions should not constitute an obstacle to the use of powerful and strong true fungicidal substances.

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Brogan, J. William, Jr., B.S., Chemistry. Teaching Assistant, Rutgers University, New Brunswick, N. J.

Brumlik, Joseph, M.D., Internal Medicine. Assistant Professor of Clinical Medicine, New York University College of Medicine, New York, N. Y.

Buchberg, Abraham S., M.D., Internal Medicine, Pulmonary Diseases. Assistant Resident in Medicine, Montefiore Hospital, New York, N. Y.

Burgunker, Mark Elias, B.A., Geology and Geophysics. New York, N. Y.

Byrd, Chester L., Jr., M.T., Virology. Research Assistant, Loyola University Medical School, Chicago, Illinois.

Carlson, Francis, Ph.D., Biophysics. Instructor, Johns Hopkins University, Baltimore, Maryland.

Caroline, Leona R., B.A., Microbiology, Mycology. Research Associate, Department of Dermatology, New York University, Bellevue Medical Center, New York, N. Y.

Chargin, Louis, M.D., Medicine. Consultant in Dermatology and Syphilology, Mt. Sinai Hospital, New York, N. Y.

Cholst, Mortimer, M.D., Ophthalmology. Resident Surgeon, Kings County Hospital, Brooklyn, N. Y.

Clark, William G., Ph.D., Physiology, Biochemistry. Chief, Pharmacology and Physiology Section, VA Center, Los Angeles, California.

Connelly, Clarence J., M.S., Psychology. Assistant to Dean, Stritch School of Medicine, Loyola University, Chicago, Illinois.

Connelly, Clarence M., Ph.D., Biophysics. Instructor, Johns Hopkins University, Baltimore, Maryland.

Corbett, James, B.S., Biology. Research Associate, Research Development Laboratories, E. R. Squibb & Sons, New Brunswick, N. J.

Cortelyou, John R., Ph.D., Experimental Embryology. Assistant Professor of Biology, De Paul University, Chicago, Illinois.

Cosla, O. K., M.D., Animal and Plant Physiology, Biochemistry. Professor of Pharmacology, College of Ozarks, Clarksville, Arkansas.

Davidson, J. Lavere, D.V.M., Veterinary Medicine. Head, Department of Veterinary Medicine, The Upjohn Company, Kalamazoo, Michigan.

Di Pasquale, Edith, B. A., Physiology. Ohio State University, Columbus, Ohio.

Drachman, Stanley R., M.D., Medicine. Resident Physician, Mt. Sinai Hospital, New York, N. Y.

Driggs, Marshall F., M.D., Medicine. Englewood, N. J.

Edgar, Margaret Thomas, B.A., Bacteriology, Research-Clinical Problems in Medicine. First Research Assistant, The American Foundation, New York, N. Y.

Ehret, Charles F., M.S., Genetics of Microorganisms, Radiobiology. University of Notre Dame, Chicago, Illinois.

Ellenbogen, Eric, Ph.D., Proteins, Peptides, Amino Acids. Postdoctorate Research Fellow, U. S. Public Health Service, Columbia University, New York, N. Y.

Espana, Carlos, Ph.D., Bacteriology. Head, Section of Virology, Research and Development Laboratories, E. R. Squibb & Sons, New Brunswick, N. J.

Fahl, James Cox., M.D., Experimental Surgery. Harrison Fellow of Surgical Research, University of Pennsylvania, Philadelphia, Pennsylvania.

Feldman, Daniel S., M.D., Neurology. Interne, Mt. Sinai Hospital, New York, N. Y.

Feldmann, Floyd Melvin, Ph.D., Public Health. Assistant to Managing Director, National Tuberculosis Association, New York, N. Y.

Fink, Colin Garfield, Ph.D., Physics and Chemistry. Professor Emeritus, Electrochemistry, Columbia University, New York, N. Y.

Fitzgerald, Emerson B., M.A., Physical Chemistry. Research Assistant, Yale University, New Haven, Connecticut.

Friedman, Sidney, M.D., Pediatrics. Chief Resident Physician, The Children's Hospital, Philadelphia, Pennsylvania.

Gargill, Samuel Leon, M.D., Internal Medicine, Endocrinology. Associate in Medicine, Harvard Medical School, Boston, Massachusetts.

Geftic, Sam Gary, B.S., Bacteriology. Bacteriologist, Ciba Pharmaceutical Co., Summit, N. J.

Gertner, Sheldon, B.S., Pharmacology. Department of Pharmacology, Yale University, New Haven, Connecticut.

Gisel, Eugene A., Ph.D., Chemistry. Head, Department of Chemistry, Fordham University, New York, N. Y.

Glockler, George, Ph.D., Physical Chemistry. Head, Department of Physical Chemistry, State University of Iowa, Iowa City, Iowa.

Gottesman, Judah Isaac, M.A., Psychology. Vocational Psychologist, Laboratory of Psychological Studies, Hoboken, N. J.

Grino, Antonio, M.D., Pathology. Assistant Attending Neurological Division, St. Vincents Hospital, New York, N. Y.

Grossman, Edward B., M.D., Medicine. Chief, Medical Service, New York Regional Office, U. S. Veterans Administration, New York, N. Y.

Hain, Katharine, H., M.D., Research in Rheumatic Fever. Assistant Pediatrician, Out-Patient Department, New York Hospital, New York, N. Y.

Harris, Charles, M.D., Medicine. Assistant Pathologist, Goldwater Memorial Hospital, New York, N. Y.

Higbie, Howard E., Ph.D., Physical Chemistry. Chemist, M. W. Kellogg Company, Jersey City, N. J.

Higgy, Jean E., B.S., Bacteriology, Immunology. Graduate Assistant, Department of Bacteriology, Ohio State University, Columbus, Ohio.

Hoffmann, George T., M.D., Pathology. Research Associate, St. Vincents Hospital, New York, N. Y.

Hough, Charles R., Ph.D., Rare Earth Chemistry. Assistant Professor of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, N. Y.

Humphreys, Roderick J., M.D., Cardiovascular Disease. Clinical Research Fellow, College of Medicine, University of Vermont, Burlington, Vermont.

Irwin, Samuel, B.S., Pharmacology. Research Assistant, Department of Pharmacology, University of Michigan, Ann Arbor, Michigan.

Johnson, Edwin Peter, Ph.D., Animal Pathology. Animal Pathologist, Virginia Agricultural Experiment Station, Blacksburg, Virginia.

Johnson, Linares B., B.A., Pharmacology. Research Assistant, Department of Pharmacology, University of Michigan, Ann Arbor, Michigan.

Johnson, Ralph M., Ph.D., Cancer Research. Research Associate, Detroit Institute of Cancer Research, Detroit, Michigan.

Jolliffe, Leslie S., M.D., Pathology. Pathologist, Lawrence General Hospital, Lawrence, Massachusetts

Kalnitsky, George, Ph.D., Intermediary Metabolism, Enzymes. Assistant Professor of Biochemistry, College of Medicine, State University of Iowa, Iowa City, Iowa.

Kass, Edward H., M.D., Infectious Diseases, Bacteriology, Immunology. Research Fellow in Medicine, Harvard University School of Medicine, Boston, Massachusetts.

Kaufman, Seymour, Ph.D., Biochemistry. Research Fellow, Department of Pharmacology, New York University, New York, N. Y.

Kaye, Robert, M.D., Infant Respiratory Physiology, General Pediatrics. Instructor in Pediatrics, University of Pennsylvania, Philadelphia, Pennsylvania.

Kelly, Alma C., Ph.D., Biology, Psychology. Director of Neuro-Somatic Reconditioning Program for Lawton Foundation, New York, N. Y.

Kostant, George H., M.D., Medicine. Assistant Adjunct, University Hospital, New York University, Bellevue Medical Center, New York, N. Y.

Knock, Frances E., Ph.D., High Polymer Chemistry. Research Associate in Pharmacology, University of Illinois, Chicago, Illinois.

Krane, Stephen M., B.A., Medicine. College of Physicians and Surgeons, Columbia University, New York, N. Y.

Lawrence, H. Sherwood, M. D., Immunology. Instructor in Medicine, New York University College of Medicine, New York, N. Y.

Lehmus, Harold J., M.D., Medicine. Assistant Superintendent, Rheumatic Fever Section, State Sanatarium, No. Wilmington, Massachusetts.

Leiner, George C., M.D., Internal Medicine, Pulmonary Physiology. Attending Physician, Hal-

loran V.A. Hospital, Staten Island, New York N. Y.

LeMaistre, Charles Aubrey, M.D., Medicine. Fellow in Medicine, Cornell University Medical College, New York, N. Y.

Leonardow, Leonard, E. E., Engineering. President, Autex Corporation, New York, N. Y.

Levin, Simon Eugene, Ph.D., Bacteriology, Biochemistry. Research Associate, E. R. Squibb & Sons, New Brunswick, N. J.

Levy, Lester Morton, M.D., Endocrinology. Fellow, Philadelphia General Hospital, Philadelphia, Pennsylvania.

Ley, Herbert L., Jr., M.D., Virus and Rickettsial Diseases, Biochemistry. Assistant Chief, Chemotherapy Research Section, Army Medical School, Washington, D. C.

Lynes, Thomas Edward, B.S., Pharmacology. Assistant Pharmacologist, Maltbie Laboratories, Incorporated, Morristown, N. J.

Machurek, Joseph E., B.S., Organic Chemistry. Research Assistant, Flushing, N. Y.

Madison, Leonard L., M.D., Metabolic Diseases. Visiting Investigator, Rockefeller Institute for Medical Research, New York, N. Y.

Mark, Harris J., M.Sc., Bacteriology. Bacteriologist, School of Public Health, Columbia University, New York, N. Y.

Martin, Frederick J., Ph.D., Physical Chemistry. Chemist, M. W. Kellogg Company, Jersey City, N. J.

Matoltsy, Alexander G., M.D., Biochemistry, Cytochemistry of Skin. Research Associate in Dermatology, Harvard University, Boston, Massachusetts.

Mermann, Alan C., M.D., Pediatrics, Hematology. Senior Assistant Resident Pediatrician, The New York Hospital, New York, N. Y.

Miller, George E., M.D., Water and Electrolyte Metabolism. Research Fellow in Medicine, University of Buffalo School of Medicine, Buffalo, N. Y.

Moreau, Louis, M.D., Cellular Physiology. Senior Assistant Surgeon, U. S. Public Health Service, Philadelphia, Pennsylvania.

Mueller, Johannes, Ph.D., Organic and Biochemistry. Postdoctorate Research Fellow, Cornell University Medical College, New York, N. Y.

Nadel, Eli, M.D., Pathology. Surgeon, U. S. Public Health Service, National Cancer Institute, Bethesda, Maryland.

Nixon, C. William, M.S., Histology, Cytology, Herpetology. Assistant in Biology, Brown University, Providence, Rhode Island.

Oester, Y. T., Ph.D., Pharmacology, Toxicology. Associate Professor and Acting Chairman, Department of Pharmacology, Loyola University School of Medicine, Chicago, Illinois.

Orbison, J. Lowell, M.D., Experimental Pathology. Assistant Professor of Pathology, Western Reserve University School of Medicine, Cleveland, Ohio.

Owades, Joseph L., Ph.D., Chemistry. Chemist, The Fleischmann Laboratories, New York, N. Y.

Patelski, Ray A., Ph.D., Organic and Biochemistry. Coordinator, New Products Development, Charles Pfizer & Company, Inc., Brooklyn, N. Y.

Peele, Talmage L., M.D., Neuroanatomy, Neurophysiology. Associate Professor of Anatomy, Duke University, School of Medicine, Durham, North Carolina.

Peiss, C. N., Ph.D., Physiology, Enzymology. Postdoctoral Fellow and Principal Investigator, Office of Naval Research, Baltimore, Maryland.

Perry, Richard L., M.D., Internal Medicine. Interne, Roosevelt Hospital, New York, N. Y.

Pfeiffer, John B., Jr., M.D., Medicine. Instructor in Neurology, Duke Hospital, Durham, North Carolina.

Rees, Thomas, M.S., Organic Chemistry. Research Chemist, Calco Chemical Division, American Cyanamid Company, Bound Brook, N. J.

Ripstein, Charles B., M.D., Experimental Surgery. Associate Professor of Surgery, Long Island College of Medicine, Brooklyn, N. Y.

Ritter, Joseph A., M.D., Pediatrics. Associate Professor, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Robertson, Charles W., M.D., General Surgery Instructor, Boston University, Boston Massachusetts.

Robinson, George, M.D., Medicine. Resident, Department of Surgery, Mt. Sinai Hospital, New York, N. Y.

Rose, Morton H., M.D., Internal Medicine, Cardiology. Instructor in Clinical Medicine, George Washington University Medical School, Washington, D. C.

Rosen, Samuel, M.S., Bacteriology, Mycology. Bacteriologist, Pyridium Corporation, Yonkers, N. Y.

Rosenblum, Ira, B.S., Pharmacology. Yale University, New Haven, Connecticut.

Rosenkranz, George, D.Sc., Organic Chemistry. Vice-President in charge of Research and Production, Syntex, S.A., Mexico, D.F.

Rowe, Charlotte, Ph.D., Biology, Physiology, Serology. Senior Technician, Westchester County Department of Laboratories and Research, New Rochelle, N. Y.

Rutstein, David D., M.D., Water Balance in Relation to Cardiovascular Disease. Professor of Preventive Medicine, Harvard University Medical School, Boston, Massachusetts.

Ryan, John D., M.D., Surgery, Medicine. Instructor in Surgery, New York University College of Medicine, New York, N. Y.

Scheider, Alfred, B.S., Horticulture. Secretary and Treasurer, Max Schling Incorporated, New York, N. Y.

Schmidt, Jack Russell, M.S., Chemotherapy of Viral Diseases. Research Associate, Department

of Medical Microbiology, University of Wisconsin, School of Medicine, Madison, Wisconsin.

Schupak, Eugene, B. A., Chemistry. Boston University, Boston, Massachusetts.

Schwartz, Benjamin S., M.A., Bacteriology, Virology. Bacteriologist, Warner Institute for Therapeutic Research, New York, N. Y.

Shaw, Saul, C. E., Engineering. Head, Saul Shaw & Company, Newark, N. J.

Shelton, Emma, Ph.D., Cytology. Cytologist, National Cancer Institute, Bethesda, Maryland.

Sherman, John F., B.S., Pharmacology. Yale University, New Haven, Connecticut.

Shumsky, Milton, M.A., Clinical Psychology, Senior Graduate Assistant, Department of Business Psychology, New York University, New York, N. Y.

Silver, Harold M., M.D., Medicine. Interne, Bellevue Hospital, New York, N. Y.

Silverman, Hirsch L., M.A., Psychology. Assistant Professor, Rutgers University, New Brunswick, N. J.

Smith, Wilbur A., M.D., Biology. Assistant Medical Director, Equitable Life Assurance Society, New York, N. Y.

Spencer, Joseph N., Ph.D., Pharmacology. Research Pharmacologist, Pharmaceutical Research Division, Commercial Solvents Corporation, Terre Haute, Indiana.

Steinberg, Marvin D., Pod.D., Neoplastic Diseases. New York, N. Y.

Stern, Kurt, M.D., Pathology. Assistant Director, Mt. Sinai Medical Research Foundation, Chicago, Illinois.

Stevens, Marion L., B.S., Biology, Bacteriology. Bacteriologist, Research Department, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Streicher, Eugene, M.A., Neurophysiology. Physiologist in Medical Division, Army Medical Center, Maryland.

Tavormina, Peter A., Ph.D., Biochemistry. Research Biochemist, Sharp & Dohme, Incorporated, Glenolden, Pennsylvania.

Taymor, Robert C., M.D., Cardiovascular Diseases. Resident, Fifth Medical Service, Boston City Hospital, Boston, Massachusetts.

Tolbert, Bert M., Ph.D., Chemistry. Research Chemist, Radiation Laboratory, University of California, Berkeley, California.

Touroff, Arthur S. W., M.D., Surgery. Attending Surgeon, Mt. Sinai Hospital, New York, N. Y.

van der Meulen, P. A., Ph.D., Chemistry. Director, School of Chemistry, Rutgers University, New Brunswick, N. J.

van Wessem, G. C., Ph.D., Medicinal Chemistry. Senior Chemist, William R. Warner and Co., Harrison, N. Y.

Villat, Henri, D.Sc., Fluid Mechanics. Director of the Institute of Mechanics, Professor, University of Paris, Paris, France.

Wagley, Philip F., M.D., Internal Medicine. Resident Physician, Johns Hopkins Hospital, Baltimore, Maryland.

Wagner, Bernard M., M.D., Cellular Physiology. Interne, Philadelphia General Hospital, Philadelphia, Pennsylvania.

Warmbrand, Hattie, B.A., Biochemistry. Research Technician in Renal Physiology, New York, N. Y.

Weatherby, Jesse Howell, Ph.D., Pharmacology, Membrane Permeability. Associate Professor of Pharmacology, Medical College of Virginia, Richmond, Virginia.

Wexler, David J., M.D., General Surgery. Attending Surgeon, Southside Hospital, Bay Shore, L. I., N. Y.

Wineburg, Elliot N., M.A. Psychology. Teaching Fellow, Hunter College, New York, N. Y.

Wisseman, Charles L., Jr., M.D., Infectious Diseases, Chemotherapy. Assistant Chief, Chemotherapeutic Section, Army Medical Center, Washington, D. C.

Wohl, Herbert, B.A., Bacteriology. Department of Bacteriology, Columbia University, New York, N. Y.

Yaverbaum, Sidney, M.S., Bacteriology. Graduate Assistant, University of Ohio, Columbus, Ohio.

Zimmerman, Irving A., M.D., Medicine. Physician, Staff of Maimonides and Kings County Hospitals, Brooklyn, N. Y.

## STUDENT MEMBERSHIP

Alpert, Norman, B.A., Physiology. Columbia University, New York, N. Y.

Cuchie, Frank T., Pharmacology. Research Assistant, Merck Institute for Therapeutic Research, Rahway, N. J.

Deschner, Eleanor E., B.A., Bacteriology. Fordham University, New York, N. Y.

Shipper, Harvey, M.D., Pediatrics. School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Weinstein, Bernard R., B.S., Physiology. Department of Physiology, University of Illinois, College of Medicine, Chicago, Illinois.